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Review article

Polymyalgia rheumatica and giant cell arteritis

Martyn Patel, MRCP, Duncan R. Forsyth, MA, FRCP *

Department of Medicine for the Elderly, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

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ABSTRACT

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are closely related conditions of unknown etiology. Both are characterized by older age at onset, being more common in women, evidence of systemic inflammation, and generally responding well to corticosteroids. Controversy remains as to whether they are two different conditions or two ends of the spectrum of a single disease. Few population-based studies have evaluated the epidemiology of PMR because of lack of a universally accepted diagnostic and classification criteria. PMR and GCA are one of the commonest reasons for long-term corticosteroid therapy in older age. Newer therapies for these conditions have been evaluated, including conventional antirheumatic disease-modifying drugs as well as newer biologics. Vascular risk factors should be modified as patients with GCA suffer an increased number of cerebrovascular events. PMR and GCA cause significant morbidity and mortality, so it is important for general practitioners and geriatricians to recognize them early. There is increased recognition of a need for long-term follow-up for aortic aneurysm development and large vessel involvement.
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1. Polymyalgia rheumatica

Polymyalgia rheumatica (PMR) is an inflammatory condition of unknown etiology mainly affecting people older than 50 years. It is a clinical syndrome characterized by

- Aching and stiffness in the neck, shoulders and pelvic girdles,
- Systemic symptoms,
- A raised erythrocyte sedimentation rate (ESR).

It usually responds rapidly to low doses of corticosteroid and has a favorable prognosis.[1]

2. Giant cell arteritis

Giant cell arteritis (GCA) is a vasculitis of large- and medium-sized vessels mostly affecting individuals older than 50 years. Early recognition and treatment is vital to prevent blindness and other systemic complications because of occlusion and rupture of involved arteries.

3. Clinical features

PMR mostly presents with a subacute or chronic onset of aching and morning stiffness in the neck, shoulders, and pelvic girdles. Symptoms are usually bilateral and symmetric but asymmetric pain can occur.[2] Constitutional symptoms of malaise, tiredness, depression, anorexia, weight loss, and fever are common. In most cases, symptoms have been present for weeks or months before the diagnosis is established. Stiffness is usually the predominant feature; it is particularly severe first thing in the morning and after inactivity during the day. Inflammatory synovitis and joint effusions have been described.[3] Synovitis of the knees, wrists, and sternoclavicular joints is most common, and its involvement is transient and mild. Presence of persistent synovitis particularly with radiological changes of juxtra-articular osteoporosis or erosions should raise the possibility of inflammatory arthritis. Physical examination may reveal decreased range of active movement of the shoulders, cervical spine, and hips.

GCA can cause a wide range of symptoms, but most patients have clinical features related to affected arteries. Common features include headache and scalp tenderness particularly in the temporal and occipital region. Scalp tenderness is common around the temporal and occipital arteries; on palpation, the vessels are often thickened and have reduced or no pulsation.

Visual disturbance is described in 25%–50% of patients with GCA, ocular lesions are caused by occlusion of the various orbital or

* Corresponding author. Department of Medicine for the Elderly, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, CB2 0QQ, United Kingdom.
E-mail address: duncan.forsyth@addenbrookes.nhs.uk (D.R. Forsyth).

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ocular arteries.[4] Examination of visual fields, pupillary reflexes (for relative afferent papillary defect), and fundoscopy {pale swollen optic disc with hemorrhages of anterior ischemic optic neuropathy [AION]} is therefore essential. The most common ocular lesion is AION, which usually leads to complete visual loss; arteritis is responsible for 12% of AION.[5] Features suggesting arteritic AION included systemic symptoms, early elevated ESR, amaurosis fugax, and early visual loss.[5] Visual loss is the most serious feature; it is sudden, painless, and mostly irreversible. Presence of visual symptoms is a medical emergency as prompt recognition of the condition and treatment can prevent blindness.

Other symptoms of GCA include pain on chewing because of claudication of jaw muscle. Less common features include hemiparesis, peripheral neuropathy, deafness, depression, and confusion. Involvement of coronary arteries may lead to myocardial infarction. Noncranial arteries can also become involved. Large vessel involvement, including thoracic aorta, is less likely the higher the ESR (hazard ratio of 0.80 per 10 mm/hr ESR above the norm).[6]

4. Classification and diagnostic criteria

As both conditions present with wide range of systemic features and there is no single diagnostic test, a combination of findings is needed for their diagnosis. For PMR, there are a number of different criteria sets with no international consensus. That proposed by Bird et al.[7] is useful in clinical practice (Table 1). A diagnosis of PMR requires three of the seven listed features; the presence of just three features confirms a sensitivity of 92% and a specificity of 80%.[7] The American College of Rheumatology has established criteria for the classification of GCA (Table 2). These criteria ensure consistency of diagnosis and allow comparison of patient groups between different centers; however, failure to fulfill these criteria need not preclude a diagnosis of either PMR or GCA in an individual patient.[9] The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) have recently published consensus guidelines on the management of PMR[10] and GCA.[11] Evaluating each condition in turn, these guidelines not only give advice on how best to secure a firm diagnosis and when to refer to specialists but also detailed advise on the longer term monitoring of disease activity and complications. The guidelines seek to simplify an approach to diagnosis and initial management of PMR (Table 3) and GCA (Table 4), supported as much as possible by an admittedly limited evidence base.[12]

5. Relationship between PMR and GCA

PMR and GCA are considered as closely related conditions representing a spectrum of disease. These two conditions may occur independently or in the same individual, either together or separated by time. Individuals with temporal artery biopsy (TAB)-proven GCA have been described to develop features of PMR and vice versa.[1]

Table 1
Bird et al.[7] diagnostic criteria for PMR

Combination of any three criteria necessary for diagnosis
• Age more than 65 yr
• ESR more than 40 mm/hr
• Bilateral shoulder pain and/or stiffness
• Morning stiffness for more than 1 hr
• Onset of illness within two wk
• Depression and/or weight loss
• Bilateral upper arm tenderness

PMR = polymyalgia rheumatica.

Table 2
American College of Rheumatology criteria for diagnosing GCA[8]

Criterion	Definition
1. Age at onset more than 50 yr	Development of symptoms or findings beginning aged 50 yr or older
2. New headache	New onset of, or new type of, localized pains in the head
3. Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation, unrelated to atherosclerosis of cervical arteries
4. Increased ESR	ESR more than 50 mm/hr by Westergren method
5. Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell

GCA = giant cell arteritis; ESR = erythrocyte sedimentation rate; PMR = polymyalgia rheumatica.

Systemic involvement is similar in both PMR and GCA. It is difficult to maintain a practical distinction between them by clinical or histological criteria; however, no definitive conclusion can be drawn about the nature of this association.[13]

6. Epidemiology

Few population-based studies have evaluated the epidemiology of PMR because of lack of universally accepted diagnostic and classification criteria. PMR and GCA almost exclusively affect older adults and are rarely diagnosed under the age of 50 years. The estimated prevalence of PMR, in the United States, is 1 in 133 people over the age of 50 years.[14] The incidence of PMR and GCA increases with age, with a peak in those 70–80 years of age. The prevalence of PMR approaches that of rheumatoid arthritis in older age, approximately

Table 3
The British Society for Rheumatology and British Health Professionals in Rheumatology stepped approach to diagnosing PMR[10]

Steps in diagnosis and management	Definition
1. Inclusion criteria	Bilateral shoulder girdle and/or pelvic pain Morning stiffness for more than 45 min Abrupt onset Age more than 50 yr Duration more than 2 wk Acute-phase response (raised CRP/ESR)
2. Exclusion criteria	Active cancer Infection Active GCA Inflammatory (RA and other arthropathies, SLE, myopathies, other CTDs) Noninflammatory (local shoulder and hip conditions, fibromyalgia, other pain syndromes)
3. Trial of low dose steroid	Prednisolone 15–20 mg daily Clinical response in less than 1 wk (at least 70% global improvement) Lab resolution in 3–4 wk
4. Follow-up (4–6) wk	No alternative diagnosis found from thorough screen at time or presentation (include myeloma screen, autoimmune screen, TSH, CK, LFTS, calcium)
5. Diagnosis PMR likely	Gradual steroid tapering Consider bone protection

PMR = polymyalgia rheumatica; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; GCA = giant cell arteritis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; CTD = connective tissue diseases; TSH = thyroid stimulating hormone; CK = creatine kinase; LFTS = liver function tests.

Table 4
The British Society for Rheumatology and British Health Professionals in Rheumatology criteria for diagnosing GCA[11]

Steps in diagnosis and management	Definition
1. Suspect diagnosis of GCA	Apply ACR criteria as Table 2
2. Immediate initiation of steroid therapy	Uncomplicated (no jaw/visual symptoms)—prednisolone 40 mg daily Complicated (jaw/visual symptoms)—prednisolone 60 mg daily, but consider i.v. methylprednisolone 500 mg–1 g daily if evolving visual symptoms Aspirin 75 mg daily for both groups
3. Urgent referral to specialists	For specialist opinion For TAB biopsy Opthalmic assessment is suspected AION
4. Biopsy positive	Gradual steroid tapering Consider methotrexate Bone protection Monitor for large vessel involvement or relapses
5. Biopsy negative	Specialist review—if clinical suspicion or US suggests GCA or AION treat as GCA If low clinical suspicion rapid steroid taper within 2 wk and seek alternative diagnosis

GCA = giant cell arteritis; ACR = American College of Rheumatology; i.v. = intravenous; TAB = temporal artery biopsy; AION = anterior ischemic optic neuropathy; US = ultrasound.

1%.[15] Both PMR and GCA are more frequent in females than in males in all age groups. The incidence of GCA increases with latitude in the northern hemisphere, with at least a twofold increase in incidence in Scandinavian countries compared with Northwestern Spain.[16] A study of biopsy-proven GCA demonstrated an average annual incidence and prevalence of 17 and 223, respectively per 100,000 population aged 50 years or more.[17]

The characteristics of both PMR and GAC appear broadly similar in mainland China as in the Western hemisphere: 75% aged more than 65 years at diagnosis, 95% have bilateral upper arm stiffness, and 100% have a raised ESR.[18] However, generalized joint stiffness may be less common and time to diagnosis significantly longer in mainland China.[18,19] Interestingly, one small Chinese cohort found a mean age at disease onset of 43.13 years (range 28–60).[19] Both PMR and GCA appear to be less common entities in China than in the Western hemisphere.[20]

A Japanese national survey gave prevalence for GCA, in patients aged 50 years and older, of 1.47 per 100,000 population, a 100-fold less than the prevalence quoted in a western population.[21]

Studies in transplanted ethnic populations in United States have also found a lower than expected rate of GCA,[22] it is possible that this may change as these populations continue to age.[23]

7. Etiology and pathogenesis

At present, the underlying pathologic abnormality in PMR is unclear. An increasing incidence of GCA and PMR after the age of 50 years implies a relationship with aging. Aging of the immune and neuroendocrine systems may be important factors in the late onset of GCA. The higher incidence rates in Occidentals, for example, in Scandinavia, Northern Europe, or United States, and lower rates in Orientals, for example, China and Japan, support a possible genetic determinant.

A distinct prodromal event resembling influenza or viral pneumonia is often noted by patients. However, viral studies have generally produced negative results. No association has been demonstrated with viruses that induce multinucleated giant cells, such as measles, herpes simplex, Epstein-Barr, and respiratory syncytial viruses.[24,25] GCA is limited to vessels with an internal elastic lamina, and electron microscopy shows fragmentation of this with mononuclear cell accumulation compatible with cell-mediated injury. Several studies using polymerase chain reaction to detect the presence of *Chlamydia pneumoniae*, parvovirus B19, and several of the human herpes viruses in TAB specimens have yielded negative results.[26,27] Some still hypothesize the existence of a triggering antigen of unknown nature activating T-cells in the artery wall, following an immune response to infection.[28] Evidence in favor of this is a dual peak in cases of PMR and GCA in association with seasonal variation in Danish respiratory infections (specifically *Mycoplasma pneumoniae*, Parvovirus B19, and *Chlamydia pneumoniae*).[29]

A primary immunological basis for both PMR and GCA has been investigated. Circulating concentrations of interleukin-6 are increased, with normal concentrations of TNF-α both in patients with an arteritic presentation of GCA and in those presenting with PMR. A selective depletion of circulating CD8 T lymphocytes in patients with GCA has been observed in most studies. No increase in expression of human leukocyte antigen-DR has been found on circulatory CD4.[30]

8. Investigations

The characteristic laboratory abnormality seen in most patients with GCA and PMR is a high ESR; it can exceed 100 mm/hr in GCA. Less striking elevation or even normal values may occasionally be seen.[31] However, an ESR of less than 30 mm/hr is associated with a likelihood ratio of GCA of only 0.02.[32] The ESR also provides a useful means of monitoring response to the treatment; however, it must be appreciated that some elevation of the ESR may occur in otherwise apparently healthy older people. A normal ESR is occasionally found with active biopsy-proven GCA.[33] Other acute phase changes may also be present, such as increase in C-reactive protein, fibrinogen, and decrease in serum albumin concentration.[34] Other laboratory findings are nonspecific. Normocytic, normochromic anemia may be present, but the white cell count and platelet counts are usually normal. Increased hepatic enzymes, such as alkaline phosphatase may also be seen. Serological tests, such as rheumatoid factor and antinuclear antibodies are typically negative.[2]

8.1. Temporal artery biopsy

Clinicians vary in their views on the usefulness of a TAB in the management of GCA. Some suggest it is of value in confirming the diagnosis particularly when patients require long-term immunosuppressive therapies; others feel that the high false-negative rate diminishes the value of the procedure.[35] As noted in Table 3, the BSR/BHPR guidelines include a biopsy as an essential part of the diagnosis and management pathway. One-third of the patients with signs and symptoms of GCA may have a negative TAB, which may be because of localized involvement of arteries in the head and neck. The “skip” lesions are seen in about one-third of the biopsies; some segments showing active disease are as short as 350 mm.[36]

Various factors can influence the biopsy result, such as size of the biopsy, number of sections examined, and the duration of the corticosteroid therapy before the biopsy. Biopsy is most useful if performed within 24 hours of starting steroids. The changes of arteritis can be seen several days after the initiation of corticosteroid therapy.[37] Therefore, one should not delay the treatment for the sake

of biopsy. A negative biopsy does not exclude GCA; however, it remains the gold standard test for confirming GCA and should be considered in all case where possibility of GCA cannot be excluded clinically.[38]

8.2. TAB-negative GCA

Those patients in whom the clinical presentation, including the response to treatment is strongly suggestive of GCA despite the negative biopsy are considered to have biopsy-negative GCA.[39]

8.3. Imaging in GCA

Ultrasound (US) examination of the temporal and occipital arteries in patients with GCA can detect abnormalities, such as reduced blood flow, stenoses, occlusions, and a "halo" surrounding the lumen of the vessel.[40] Most of these changes are nonspecific; however, the halo sign has been shown to have a specificity of 100% in one study.[41] There is no recognized role for joint US in diagnosis of PMR, although US has been proposed as a way of confirming large joint (shoulder and hip) synovitis,[42] as has shoulder magnetic resonance imaging.[43]

Angiographic examination of the aortic arch and its branches may show abnormalities among those with features of large artery involvement.[44] Magnetic resonance imaging and computerized scanning can also detect large artery involvement; however, overall vascular changes are not as clearly demonstrated as with angiography. The BSR/BHPR guidelines recommend aortic imaging at time of diagnosis of large vessel GCA and subsequent biannual chest radiography to look for thoracic aortic arch widening.[11]

Positron emission tomography can detect the presence of subclinical inflammation of the large vessels as shown by high uptake of radiolabeled glucose analog in some cases of GCA and PMR.[45]

The use of imaging in the management of GCA has not yet changed the clinical practice concerning the requirement of a TAB.

9. Pathology

Large- and medium-sized arteries are affected, the involvement is patchy, and skip lesions are often found. There is preferential involvement of muscular arteries with well-developed internal and external elastic laminae. The histological appearance in GCA is characteristic with panarteritis and giant cell granuloma formation, often in close proximity to a disrupted internal elastic lamina. The adventitia is usually invaded by mononuclear, and occasionally polymorphonuclear, inflammatory cells.

There has been little to support a concept of primary muscle disease in PMR. Serum aldolase and creatine phosphokinase are normal, and there is no abnormality on electromyography. Muscle biopsy has shown Type II atrophy alone and there is no evidence of inflammatory changes.[46]

10. Differential diagnosis

The differential diagnosis in an older person with muscle pain, stiffness, and an increased ESR is wide, as many other conditions can present in a similar fashion (Table 5). It is important to rule out any underlying infection, malignancy, or inflammatory arthritis. The value of a careful history and examination in the assessment of these patients cannot be overemphasized.

11. Management

Early diagnosis and treatment with corticosteroids is most important in the treatment of GCA; they rapidly relieve the symptoms and reduce the incidence of complications, such as blindness. The response to corticosteroids is usually dramatic and occurs within days. Corticosteroid treatment has improved the quality of life for patients, although there is no evidence that treatment reduces the duration of the disease. Initially, steroids should be given in a dosage sufficient to control the disease. In practice, most studies report starting with 10–20 mg prednisolone daily to treat PMR and 40–60 mg for GCA.[47] Reducing the dose of steroids too quickly may result in a flare-up of symptoms. The aim is to wean the patient off steroids or find the minimum maintenance dose required to relieve symptoms and suppress the ESR (Boxes 1 and 2). The use of intravenous methylprednisolone at a dose of 500 mg–1 g daily for three days is recommended only for complicated GCA (where there is evolving visual loss, history of amaurosis fugax, or tongue claudication).[48,49]

Up to 50% of patients will be able to discontinue steroids after two years and some may take longer.[50,51] Relapses are most likely in the first 18 months of treatment, but they can occur after apparently successful treatment when corticosteroids have been discontinued. At present, there is no way of predicting those patients most at risk. Diagnosis of relapse should be made on the basis of clinical features because the ESR and C-reactive protein concentration are often not increased during relapses or may be increased as a result of other causes. However, where symptoms recur and the acute phase proteins are normal, the possibility of other comorbid conditions being responsible for the symptoms must be considered. The biomarker procalcitonin has been favorably evaluated for use as a tool to distinguish bacterial systemic sepsis from an autoimmune disease flare[52] but is yet to enter widespread clinical practice outside of the intensive care setting.

Patients who are unable to "wean-off" prednisolone because of recurring symptoms, or who develop serious corticosteroid-related side effects, pose particular problems. Various drugs, such as methotrexate and azathioprine have been tried for their steroid sparing effect; however, overall consensus is that, the benefit is only

Table 5
Differential diagnosis of PMR

Differential diagnosis of PMR	
Soft tissue lesions	Rotator cuff lesions, adhesive capsulitis
Joint disease	Osteoarthritis, rheumatoid arthritis
Connective tissue diseases	
Infections	Localized and systemic
Muscle disease	Myopathy, polymyositis
Bone disease	Osteomalacia
Hypothyroidism	
Parkinsonian syndromes	
Neoplastic disease	Multiple myeloma, lymphoma
Fibromyalgia and regional pain syndromes	
Functional	

PMR = polymyalgia rheumatica.

Box 1. Steroid regime for polymyalgia rheumatica

- Start prednisolone 15–20 mg once daily for four weeks and monitor clinical response.
- Reduce prednisolone by 2.5 mg every four weeks until down to 10 mg daily.
- Further reduction by 1 mg every four weeks until down to minimum maintenance dose of 5–7.5 mg daily.
- Continue maintenance dose for 6–12 months.
- Finally reduce by 1 mg every four weeks and stop.
- Some patients may require a much longer or even lifelong treatment on a low dose.

Box 2. Steroid regime for giant cell arteritis

- Start prednisolone 60 mg once daily for 6–8 weeks and monitor clinical response.
- Reduce prednisolone by 5 mg every week until down to 20–30 mg.
- Reduction by 2.5 mg every two weeks until down to 10 mg once daily.
- Further reduction by 1 mg every four weeks until down to minimum maintenance dose of 5–7.5 mg daily.
- Continue maintenance dose for 6–12 months.
- Finally reduce by 1 mg every four weeks and stop.
- Some patients may require a much longer or even lifelong treatment on a low dose.

modest.[53] Nonetheless, these should be tried. Methotrexate appears to have the best evidence[54] and is endorsed in the recent BSR/BHPR guidelines particularly for use in GCA. Most of the published studies have a relatively small number of patients, with a short duration of follow-up and high numbers withdrawing from treatment. Anecdotal studies with infliximab have shown its effectiveness in reducing need for high dose steroids in otherwise treatment resistant cases of PMR; however, number of patients in these was very small.[55]

Long-term use of oral corticosteroids is associated with loss of bone mineral density and increased fracture risk, particularly in sites rich in trabecular bone.[56] Bone loss occurs early in the course of treatment, although risk of fracture is roughly associated with cumulative steroid dose. It has been estimated that 30%–50% of long-term users of corticosteroids will experience a fracture,[57,58] and the associated morbidity after such an event is substantial.[59] Both GCA and PMR require long-term corticosteroid therapy and these patients should be started on appropriate preventive therapy for steroid-induced osteoporosis to avoid added morbidity and mortality from fractures.[60]

There appears to be an increased incidence of cerebrovascular events with GCA,[61] especially in the vertebrobasilar territory.[62] British guidelines now recommend using patient appropriate antithrombotic therapy.[11]

Regular urinalysis for glycosuria and checks for hypertension should also be performed while patients remain on steroids.

12. Overview of management of PMR and GCA

1. Consider GCA in all patients with PMR.
2. Prescribe steroids early to relieve symptoms and prevent complications.
3. Ensure that patients with PMR or GCA seek urgent medical attention if they develop new visual symptoms.
4. Monitor response to treatment clinically and with changes in inflammatory markers.
5. Always consider other possible diagnosis if symptoms do not improve with steroid treatment.
6. If symptoms worsen or reappear, increase the dosage of steroids to the dose that previously controlled the symptoms.

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